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C - Reactive Protein as A Predictor of Sepsis in Children Up to 5 Years of Age

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ABSTRACT

Objective: To determine frequency of raised CRP levels in children clinically diagnosed to have sepsis.
Patients and Methods: In this cross-sectional study, a total of 91 children up to 5-year age, clinically diagnosed as having sepsis, were enrolled and were screened for a raised CRP level. The outcome of the study was recorded as the frequency of raised CRP level in children clinically suspected of having sepsis.
Results: The results of the study showed that 95.6% (87/91) of our patients had a raised CRP level.
Conclusion: CRP can be used as an early sensitive tool for diagnosis of bacterial sepsis.
Key words: Biomarkers, C- reactive protein, Sepsis.

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[1]Conception, Synthesis and Planning of the research, Interpretation and analysis *[2,3]Active participation in active methodology & Discussion,[4] Review the study.*	*Dr. Itrat Fatima* *itratfatima012@gmail.com*	*Received: Feb 14, 2017* *Accepted: Mar 15, 2017*

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Introduction

C-reactive protein (CRP) is an acute-phase reactant whose level in the serum rises with inflammation. It is of hepatic origin and is a protein that increases following IL-6 secretion by macrophages,[1] in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral or fungal infections, rheumatic disorders, autoimmune disorders, malignancies and conditions causing tissue injury and necrosis.[2] CRP rises within 6 hours of the onset of inflammation and may rise up to 10, 000 folds peaking at 48 hours. It has a half-life of about 19 hours which is constant and hence its level is determined by its rate of production and therefore by the severity of the precipitating cause.[3] It may be concluded that CRP is a good indicator of inflammation and may be used to screen for inflammation. Evaluations have been done to determine its diagnostic strength in this context.[2]

CRP is an abnormal protein as it is not found in the serum of a healthy person, but increases in a matter of hours after onset of tissue damage or destruction, regardless of the cause, and disappears equally rapidly after the destructive process has ceased. CRP is not subject to normal variation, as is the erythrocyte sedimentation rate (ESR) and is independent of the hematocrit. In this respect, it is generally found to be more useful and sensitive marker of acute inflammatory disease than ESR.[4]

Combined usage of total leucocyte count (TLC) and CRP gives a better positive predictive value in the diagnosis of inflammatory conditions.[5] CRP is not only useful in determining the presence of an inflammatory disease but is also helpful in following its progress and effectiveness of treatment. In particular serial measurements of CRP is

very useful, for instance when one has to decide about the duration of antibiotic therapy in infections.[6-10] The present study was conducted to determine the frequency of raised levels of qualitative CRP in children clinically suspected of having sepsis in our setup.

Patients and Methods

This cross-sectional study was conducted at the Children's Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad. The sample size was calculated as 91 by WHO sample calculator with an anticipated population of 17% at 95% confidence level and absolute precision of 0.07. A total of 91 children up to 5 years of age clinically suspected of having septicemia were enrolled by non-probability consecutive sampling. Children with liver disease, trauma, chronic kidney disease, suspected rheumatic disease or other focal infections like pneumonia, urinary tract infections were excluded from the study. Clinical impression of sepsis was made if the patient had several of the considered signs and symptoms of sepsis namely fever, reluctance to feed, lethargy, purpura/bleeding or altered level of consciousness. Approval from the hospital ethical committee was taken. An informed written consent was taken from parent/caregiver after explaining the importance of the study. Patient profile including name, age sex, address, hospital number, serial number, date of inclusion in the study were noted. If the patient was sick, he /she was first stabilized before blood samples were taken for TLC and CRP levels. All information was collected and entered into a proforma especially designed for this study. The data was analyzed on a computer using SPSS version 10. Mean was calculated for numerical variables like age and total leukocyte count. Frequency and percentages were presented for categorical variables i.e. gender, positive CRP. CRP >5mg/dl was taken as positive.

Results

In our study a total of 91 cases clinically suspected of having sepsis were enrolled. The mean age of the patients was 2.6 years ranging from 0.1 to 5 years. Among these, 41 (45%) of the patients were between 3 and 5 years, 24(26.4%) were less than 1 year and 26(28. 5%) were between 1 to 3 years. There were 54 (59%) males and 37 (41%) females with a male to female ratio of 1.4:1. As regards clinical signs and symptoms of sepsis, almost all patients 88(96.7%) had a fever. Other significant clinical findings were purpura/bleeding from different sites in 57 (62.2%), reluctance to feed in 51(56%), lethargy also in 51 (56%), poor tolerance to feeding in 33(36.2%) and altered level of consciousness in 24(26.3%)–Figure 1.

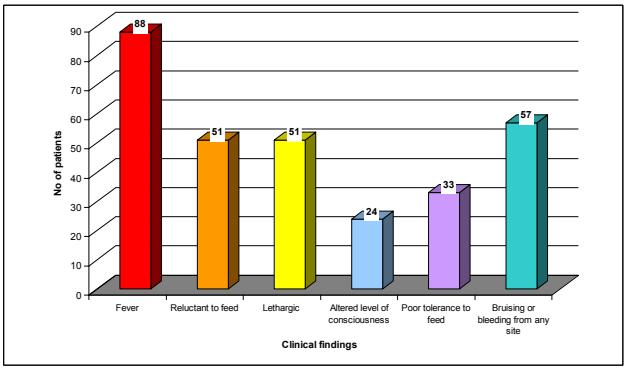

Figure 1: Clinical findings in study patients (N = 91)

Total leucocyte count was measured in all the study patients. The mean TLC was 18713/cmm ranging from 13400 to 30000/cmm. Majority of the patients- 56(61.5%) had TLC between 15001 and 20000cmm, 19(20.8%) had TLC between 13000 and 15000/cmm whereas 10(10.9%) had TLC between 20001 and 25000/cmm and 6 (6.5%) were found to have TLC between 25001 and 30000/cmm- Table 1.

Table 1. Total Leukocyte Count in the study patients (N = 91)

TLC (cmm)	Number (%)
13000 to 15000	19 (20.9)
15001 to 20000	56 (61.5)
20001 to 25000	10 (11)
25001 to 30000	6 (6.6)

As per our study objective the frequency of raised CRP was measured in all the patients. Vast majority of the patients- 87(95.6%) were found to have an increased CRP level while in only 4(4.4%) patients, CRP was not raised- Table 2.

Table 2: CRP findings in study patients (n = 91)

C-reactive protein	Number (%)
Increased	87 (95.6)
Not increased	04 (4.4)

Discussion

CRP has been fairly extensively studied as a useful marker of bacterial sepsis in neonates and children. [11-15] Other studies which have also reviewed the same.[16, 17] Ammo K et al prospectively studied the utility of CRP and ESR as a diagnostic marker for sepsis in neonates, evaluating 293 episodes of sepsis in 163 infants.[18] Complete blood counts with differentials, blood cultures, CRP and ESR were measured. As expected hematologic profile of sepsis episodes were characterized by higher white blood cell counts among other indices. In their study the CRP and ESR in combination with absolute neutrophil count had the highest negative predictive value (93%) for ruling out sepsis and 95% sensitivity for diagnosing sepsis. They concluded that CRP and ESR are highly sensitive markers for neonatal sepsis and recommended prospective studies incorporating CRP and ESR into a sepsis scoring system. In comparison, our study though not confined to neonates, had a number of neonates as part of the study population. Though we did not evaluate the data of neonates separately but in general we also concluded that raised TLC and CRP levels were present in the vast majority of patients clinically diagnosed to have sepsis. Sidra Younis et al also studied the diagnostic accuracy of CRP in neonatal sepsis.[12] They enrolled 59 consecutive patients with risk factors and clinical features suggestive of sepsis. CRP and blood cultures were taken from all patients. In their study, the sensitivity, specificity, positive predictive value and negative predictive value of raised CRP were found to be 97.3%, 95.2%, 97.3% and 95.2% respectively. Blood cultures were positive in 64.4% and raised CRP was found in 64.5% cases. They concluded that CRP has high sensitivity and specificity for establishing the diagnosis of neonatal sepsis which is comparable to that of blood culture results. In comparison, our study only included patients who were clinically diagnosed to have sepsis and CRP was not compared to blood cultures and this was a limitation of our study.

Michal Kyr et al studied the role of the time course of CRP levels in association with clinical outcomes in children with different septic conditions in an intensive care environment.[19] They performed a retrospective analysis of 99 patients with inflammatory response syndrome, sepsis or septic shock syndrome. They monitored the CRP level for 10 days following the onset of the septic condition and determined that there is a significant effect of septic condition and diagnosis on the course of CRP levels. In patients who did not progress to septic shock, CRP blood levels decreased rapidly after reaching peak values in contrast to the values in patients with septic shock in whom CRP levels decreased slowly. They concluded that the more severe the systemic reaction to the insult, the higher and the more prolonged the CRP levels. Their study population had an average age of 7.6 years with a range of 0.1-18.5 years an age range which was much higher than in our study (mean age, 2.6 years with a range of 0.1-5 years). Moreover, we did not do quantitative or serial CRP levels in our study. Both studies emphasize the role of CRP in sepsis, however, the study by Michal Kyr et al goes a step further in evaluating the role of serial measurements of CRP and understanding the pattern of change in levels of CRP and relating it to sepsis severity.

Lanziotti et al published an excellent review on the use of biomarkers in the screening, diagnosis, prognosis (risk stratification), monitoring of therapeutic response and rationale use of antibiotics (e.g. determining the adequate treatment length) in children with sepsis.[20] Their emphasis was on evaluating the role of CRP, procalcitonin, interleukin 6, 8 and 18 and a few other markers in this context. They evaluated five main publications on the use of CRP in pediatric infection/sepsis and concluded that the use of biomarkers, including CRP, in pediatric sepsis cases is promising, although their use should always be correlated with clinical evaluation.[21-25] They emphasized that combined use of multiple biomarkers has a much better sensitivity and specificity in the diagnosis and prognosis of sepsis compared to the use of a single biomarker. In their view biomarkers, such as CRP and procalcitonin have shown a key role in clinical practice and CRP is especially useful for the evaluation of the response to antibiotic treatment when evaluated serially. Other advantages of CRP that they enumerated were that it is easily available, has low cost, peaks 36-50 hours after an inflammatory trigger and is not affected by immunosuppression, renal dysfunction or corticosteroid use. They also sited limitations of CRP testing in that it has variable sensitivity for detecting bacterial infections (lower when a single level is measured) and also that it

has low accuracy. Thus, they concluded that the dynamic and judicious use of CRP combined with clinical criteria and/or other biomarkers has great value and should be considered in sepsis diagnosis and especially in sepsis treatment evaluation where it probably has a better role than in the diagnosis.

Our study certainly had a number of limitations. Firstly, it was a descriptive series only looking at the frequency of raised CRP levels in children clinically suspected of having sepsis. A control group or a validating test like blood culture would have helped to measure actual accuracy. Selection bias always remains a possibility in observational studies with convenient sampling procedures. Moreover, we did not do quantitative or serial CRP measurements as were done in most of the above-cited studies. However, our study did carry the advantages of being the first study of its kind in our local setting, including a number of neonatal and preschool children in the study population and using an easily available low cost test like CRP and determining whether it could be used as an early surrogate marker of infection in children clinically suspected of having sepsis.

Conclusion

In children, up to 5 years of age clinically suspected of having sepsis a raised total white cell count along with a raised CRP are present in the vast majority and therefore these two indicators together may be used as early surrogate markers of sepsis in this paediatric age group. Better powered studies are needed in our setup to validate this conclusion.

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